Remarks

Claims 1-44, 49, 50, 53, 57 and 58 are pending in the application. Claims 1, 17, 36, 37, 38, 41 and 43 were amended to correct the spelling of "occurrence." Claim 2 was amended to provide proper antecedent basis. Claims 34, 36, 37 and 38 were amended to correct inadvertent errors. Claims 39, 42 and 44 were amended to include the definitions for substituents that the claims referred to in a previous claim. Each of the amendments are described in more detail below. Applicant respectfully request reconsideration of the claims based on the following arguments and the amendments to the claims.

35 USC §112 Rejections

I. Claims 1-35, 38-44, 49, 50, 53, 57 and 58 were rejected under 35 USC §112, 1st paragraph as being non-enabled.

Examiner asserts that the scope of "prodrug" is not adequately enabled and no guidance is provided as to how the compounds are made more active *in vivo*. Applicants respectfully disagree with Examiner's assertions. First, prodrugs are not by design more "active" than the compound from which the prodrug is made. As defined in the specification on page 27, lines 22-25, the term "prodrug" means a compound that is transformed *in vivo* to yield a compound of Formula (I) or a pharmaceutically acceptable salt, hydrate or solvate of the compound. Hence, the activity is determined by the activity of the compound and not the prodrug of the compound.

Applicants respectfully submit that the present Specification also meets the statutory requirement for prodrugs as evidenced by the disclosure. Applicants have described several alternative methods of making prodrugs in the written description on page 27, line 30 through page 29, line 2. Several different types of prodrugs are described (e.g., functionalized carboxylic acids, alcohols, and amines) with representative descriptions of each functional prodrug. In addition, a reference is provided which provides detailed guidance on how to choose and make the desired prodrug. See, page 27, lines 25-29. Those skilled in the art are well aware of when and how to make prodrugs to acquire a desired

effect which will depend upon the particular purpose for which the drug is to be used. Applicants provide more than ample guidance to direct the reader on how to make the prodrugs through general guidance and the cited reference. In addition, there are only limited sites on the compounds as claimed that would lend themselves to the production of prodrugs; therefore, there is no undue experimentation to identify and make the desired prodrug.

It is well established that an inventor is not required to exemplify every species and/or embodiment of his/her invention. In fact, there is no requirement to provide any working examples. To satisfy the enablement requirement, one must provide sufficient information to enable one of ordinary skill in the art to practice the invention not a novice as implied by Examiner. To include every minute detail in the specification would be superfluous and make it difficult to identify the new or important aspects of the invention. For that reason, Applicants respectfully submit that the general description of the various functionalities that may be used for prodrugs in the specification as well as the cited reference to alternative procedures provides ample disclosure for one skilled in the art to practice the invention as claimed. Examiner has provided no specific evidence to the contrary.

II. Claims 2-16, 34, 36-39, 49 and 50 were rejected under 35 USC §112, 2nd paragraph as being indefinite.

(a) Examiner objects to the reference to hydrogen in the definition of R^4 in dependent Claim 2 since hydrogen is not included in the definition of R^4 in Claim 1. Applicant apologizes for this oversight. Claim 2 has been amended to remove the definition of R^4 being hydrogen and inserted n is 0. When n is 0, R^4 is necessarily hydrogen; therefore, the addition of "n is 0" in the claim does not introduce any new matter or change the limitation of the claim in any way. The amendment simply corrects an inadvertent drafting error.

(b) and (c) Examiner has pointed out inadvertent duplications of species in Claim 34. Applicant thanks Examiner for pointing out these errors. Claim 34 has been amended to delete the duplicate species.

(d) and (e) Examiner has pointed out another inadvertent error in Claims 36 and 37 where the preamble refers to a compound of Formula (!A) and the structure illustrated immediately below the preamble is a compound of Formula (I). This is clearly an error. Support for changing the reference in the preamble to a compound of Formula (I) may be found in the specification on page 5, lines 16-18.

(f) Claim 38 contains a format error which occurred in the previously filed amendment. The claim properly refers to "β_3" in the originally filed claims. Applicant has entered the change as an amendment even though it was never amended in the listing of claims in the previously filed amendment. It was simply a format error by the computer.

(g) Examiner asserts that the absence of steps involved in determining which diseases are capable of being mediated by inhibiting the β_3 adrenergic receptor and the exact dosage to be administered is indefinite. She goes on to assert that *in vivo* data is required in order to provide sufficient support for a method of use claim. This is clearly not the law. Clinical trial data, especially of humans, has never been required to support a method of use claim. It would be impossible to predict an exact dose without conducting extensive clinical trials for each individual compound claimed. Courts have repeatedly found that the mere identification of a pharmacological activity of a compound that is relevant to an asserted pharmacological use provides an immediate benefit to the public and thus satisfies the utility requirement. *Nelson v. Bow*ley, 626 F.2d 853, 206 USPQ 881 (1980). Similarly, courts have found utility for therapeutic inventions despite the fact that an applicant is at a very early stage in the development of a pharmaceutical product or therapeutic regimen based on a claimed pharmacological or bioactive compound or composition.

> We perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, *in vitro* testing, may establish a practical utility for the compound in question. Successful *in vitro* testing will marshall resources and direct the expenditure of effort in further in vivo testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an *in vivo* utility.

Cross v. Iizuka, 753 F.2d 1040, 1051, 224 USPQ 739, 739, 747-48 (Fed. Cir. 1985).

Clearly, Examiner's statements are contrary to existing law. Applicants have provided extensive descriptions of biological assays used to evaluate and predict the utility of the compounds of the present invention. See, page 62, line 27 through page 78, line 3 of the specification. In addition, the range of binding data observed for the compounds exemplified in Examples 1-3 are included on page 63, lines 26-28 which clearly indicate the binding affinity of the compounds to the β_3 adrenergic receptor.

In addition, Applicants would like to point out to Examiner the discussions in the specification on page 32, lines 25 through page 33, line 17; page 34, line 7 through page 36, line 31; page 38, lines 24-29; and page 38, lines 30 through page 41, line 14, Applicants describe the dosage range and various means of administration for humans as well as animals. Clearly, the exact dosage is generally dependent upon a number of factors including the health of the subject being treated, the extent of treatment desired, the nature and kind of concurrent therapy, if any, and the frequency of treatment and the nature of the effect desired. Therefore, the particular dosage and frequency of administration are better left to the attending physician or veterinarian.

Examiner implies that there is no evidence of record which would enable the skilled artisan in the identification of the patients who would benefit from the treatments claimed. Those skilled in the art (e.g., physicans and veterinarians) are quite capable of identifying patients who might benefit from the use of compounds that act as β_3 adrenergic modulators based on the magnitude of literature discussing the mechanism of action for such receptor. Inclusion of such detailed information would be superfluous. The state of the art clearly shows that β_3 adrenergic modulators are well known and have been shown to be useful for a number of indications (including those outlined in Applicants' specification on page 31, line 23 through page 32, line 24.

Examiner also asserts that there would be undue experimentation. The specification is not required to teach every detail of the invention or be so

voluminous that it becomes incomprehensible as suggested by the Examiner. Examiner has provided no specific evidence to support her allegation of undue experimentation but instead, makes conclusory statements that development of pharmaceutical drugs and compositions is a difficult and complicated process. Although Applicants agree that drug development is quite complex, that is not a proper reason for rejecting Applicants claims for being indefinite. Applicants submit that there is more than ample disclosure based on the comments above for one skilled in the art to practice the invention without undue experimentation.

In addition, the present compounds are not the first compounds in the field to have activity as β_3 adrenergic receptor modulators as evidenced by the discussion in the background of the invention and citations of prior art in the IDS. Therefore, the use of the compounds of the present invention are not uses of first impression that would require more convincing evidence of utility for an unusual or new purpose.

§103 Rejections

I. Claims 1-22, 17-27, 34, 25, 37-44, 49, 50, 53, 57 and 58 were rejected under 35 USC §103(a) as being unpatentable over Dow, US 5,977,124.

Examiner asserts that the generic structure disclosed and claimed in US 5,977,124 encompasses the compounds of the present invention. Although the claims in US 5,977,124 may dominate the compounds of the present invention, that does not preclude an applicant from acquiring an improvement patent based on such earlier disclosure (i.e., selection invention). Attached herewith, Examiner will find a declaration by Robert L. Dow (co-inventor of the present invention) that clearly shows a significant increase in functional efficacy observed by representative compounds of the present invention (EC_{50} from 0.004 to 0.01 μM) as compared to representative compounds exemplified in US 5,977,124 (0.182 to 6.16 μM). Nothing in US 5,977,124 teaches or suggests that a significant increase in functional efficacy would be observed for compounds having a terminal sulfamide group (e.g., Compounds in US 5,977,124 having Formula (I) wherein Y is $-NR^1-$ and Z is $-(CH_2)_nSO_2NR^9R^{10}$), where n is 0). Unlike the compounds of the present invention, the compounds

disclosed in US 5,977,124 require an amino group attached to either a pyridyl or pyrimidyl group at the other end of the molecule.

Even if Examiner could establish a *prima facie* case of obviousness, the data presented in the declaration clearly rebuts any such assertion.

Obviousness-type Double Patenting Rejection

I. Claims 1-11, 17-27, 34, 35, 37-44, 49, 50, 53, 57 and 58 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 12-20 of US 5,977,124.

It is well established that double-patenting does not apply where an invention covered by a later patent application is distinctly different and independent from that covered by the first patent. In addition, the Federal Circuit held in *In re Kaplan* (789 F.2d 1574, 229 USPQ 678 (Fed. Cir. 1986)) that a double patenting rejection cannot be justified solely on the ground that the subject matter of a claim in a second patent application is dominated by the claims in the first patent application. Applicants respectfully submit that although the claims in US 5,977,124 may overlap with the claims from the present application, the invention of the present application is patentably distinct from the invention claimed in US 5,977,124.

To establish a *prima facia* case of nonstatutory-type double patenting, the examiner must (1) identify the invention claimed in the claims under consideration and in the claims of the referenced patent; and (2) establish that any variation between the inventions claimed in the present application and the patent would have been obvious to a person of ordinary skill in the art. The mere assertion that the two applications are claiming common subject matter is legally inadequate. (See, *In re Kaplan*, ibid.) The examiner has failed to provide any analysis to support a *prima facia* case of nonstatutory-type double patenting; therefore, the rejection is improper and should be withdrawn.

In a good faith effort to expeditiously proceed with the prosecution, Applicants would like to point out the key distinctions between the subject-matter claimed in the present invention and the subject-matter claimed in US 5,977,124.

Although the claims of the present invention may overlap with a small subset of compounds disclosed and claimed in US 5,977,124, nothing in US 5,977,124 teaches or suggests that a significant increase in functional efficacy would be observed for compounds having a terminal sulfamide group (e.g., Compounds in US 5,977,124 having Formula (I) wherein Y is $-NR^1-$ and Z is $-(CH_2)_nSO_2NR^9R^{10}$, where n is 0). See the declaration attached herewith. In addition, the compounds disclosed in US 5,977,124 require an amino group attached to either a pyridyl or pyrimidyl group at the other end of the molecule.

Claim Objections

I. Claims 39, 40, 42, 44, 50, 53, and 58 were objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim must be stated in the alternative and a multiple dependent claim cannot depend from another multiple dependent claim.

Examiner has mistaken a reference to a definition in a previous claim as a dependent claim. It is well known practice in patent drafting to refer back to previous claims for definitions to keep the claims concise. Since Examiner objects to such practice, Applicants have amended the relevant claims to include the definitions in the claims. These amendments to the claims have not introduced any new matter or limited the claims in any manner.

Respectfully Submitted:

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